Partial and Generalized Lipodystrophy: Comparison of Baseline Characteristics and Response to Metreleptin

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Context: Lipodystrophies are extreme forms of metabolic syndrome. Metreleptin was approved in the US for generalized lipodystrophy (GLD), but not partial lipodystrophy (PLD).

Objective: To test metreleptin's efficacy in PLD versus GLD and find predictors for treatment response.

Design: Prospective, single-arm, open-label study since 2000 with continuous enrollment. Current analysis included metreleptin treatment for ≥6 months as of January, 2014.

Setting: National Institutes of Health, Bethesda, MD.

Participants: Patients clinically diagnosed with lipodystrophy, leptin <8 ng/mL (males) or <12 (females), age >6 months, and ≥1metabolic abnormality (diabetes, insulin resistance, or hypertriglyceridemia).

Intervention: Subcutaneous metreleptin injections (0.06- 0.24 mg/kg/day).

Main outcomes and measures: Change in A1c and triglycerides after 6 and 12 months of metreleptin.

Results: Baseline metabolic parameters were similar in 55 GLD (A1c, 8.4±2.3%; triglycerides, geometric mean [25th, 75th percentile], 467 mg/dL [200, 847]) and 31 PLD patients (A1c 8.1±2.2%, triglycerides 483 mg/dL [232, 856]) despite different body fat and endogenous leptin.

At 12 months, metreleptin decreased A1c (to 6.4±1.5%, GLD, $p<0.001$; 7.3±1.6%, PLD, $p=0.004$) and triglycerides (to180 mg/dL [106, 312], GLD, $p<0.001$; 326 mg/dL [175, 478], PLD, $p=0.02$). A1c and triglyceride changes over time significantly differed between GLD and PLD.

In subgroup analysis metreleptin improved A1c and triglycerides in all GLD subgroups except those with baseline triglycerides <300 mg/dL, and all PLD subgroups except baseline triglycerides <500 mg/dL, A1c <8% or endogenous leptin >4 ng/mL.

Conclusions: In addition to its proven efficacy in GLD, metreleptin is effective in selected PLD patients with severe metabolic derangements or low leptin.

The cluster of conditions that defines metabolic syndrome, namely dyslipidemia with high triglycerides and low high-density-lipoprotein cholesterol (HDL-C), dysglycemia, hypertension, and central obesity, has become a worldwide epidemic. Recent criteria define the syndrome as 3 out of 5 of the above criteria, no longer enforcing an obligatory increased waist circumference or central obesity for diagnosis (1). The characteristic pattern

Abbreviations:

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of metabolic syndrome-associated dyslipidemia as well as insulin resistance are also hallmarks of a group of rare disorders called lipodystrophies. These are characterized by either inherited or acquired loss of subcutaneous fat, extreme insulin resistance, severe hypertriglyceridemia and low HDL-C (2, 3), and hence represent an extreme variant of metabolic syndrome.

Generalized lipodystrophy (GLD) is associated with whole-body subcutaneous adipose loss, whereas depot-specific adipose loss suggests partial lipodystrophy (PLD). Low adipose storage results in very low levels of the adipokine leptin in GLD, and variably higher leptin in PLD (4), leading to altered hunger-satiety signals to the central nervous system (CNS) and hyperphagia. The caloric surplus is accumulated as ectopic fat in the liver and muscle, causing severe insulin resistance and diabetes with high insulin requirements, and hypertriglyceridemia, which may be severe enough to induce recurrent pancreatitis (5). Patients with lipodystrophy also present with a characteristic physical appearance, fatty liver disease (6), a spectrum of cardiomyopathies (7) and proteinuric nephropathies (8), and insulin resistance-associated hyperandrogenism (9–11).

Leptin administration in a mouse model of GLD was a turning point in lipodystrophy management (12). It resulted in dramatic improvement in metabolic abnormalities in the mouse, forming a rationale for studying the effects of meterleptin, a recombinant analog of human leptin, in patients. Prior to meterleptin, lipodystrophic patients were treated with conventional high-dose antidiabetic and lipid lowering drugs, mostly without achieving adequate control of their severe disease. Studies conducted at the National Institutes of Health (NIH) Clinical Center showed that meterleptin treatment reduced food intake (13) and substantially improved most metabolic abnormalities in lipodystrophy patients, studied as a cohort of all forms with no distinction between lipodystrophy subtypes (14, 15). In GLD, meterleptin dramatically decreased hypertriglyceridemia and markedly improved glycemic parameters, including fasting glucose, hemoglobin A1c (A1c) and insulin resistance (16–19). It also improved ectopic lipid storage (20), hyperfiltration and proteinuria (8) and steatohepatitis (6). In PLD, meterleptin ameliorated hypertriglyceridemia, however its effects on hyperglycemia have been conflicting (17, 21–23). Of note, due to the rarity of lipodystrophy, all studies have enrolled very small cohorts of patients (N = 7–36 GLD, N = 6–24 PLD). Nevertheless, given the convincing efficacy data in GLD, the U.S. Food and Drug Administration (FDA) approved meterleptin's use in GLD in February, 2014. However, meterleptin was not approved for use in patients with PLD, in whom the benefits were not as well established.

The overall goal of this study was to describe baseline characteristics and response to meterleptin treatment in PLD as compared to GLD. We also looked for predictors of response to meterleptin by asking (1) whether the lipodystrophy type (GLD vs. PLD) or the endogenous leptin level better predicts the response to meterleptin and (2) is there a subgroup of patients that best responds to meterleptin.

Materials and Methods

Study design

This was a prospective, one-arm open-label study evaluating effects of meterleptin in lipodystrophy. The study was conducted at the NIH (NCT00025883) and was approved by the institutional review board (IRB) of the National Institute of Diabetes and Digestive and Kidney Diseases. Written informed consent was obtained from patients or their legal guardians. Assent was obtained from participants under 18 years of age. This study has been ongoing at the NIH since 2000, with continuous enrollment and variable duration of follow-up. The current analysis includes GLD and PLD patients treated with meterleptin for $\geq$ 6 months as of January, 2014.

Patients

Inclusion criteria were: a clinical diagnosis of lipodystrophy, low serum leptin at study enrollment ($<$8 ng/mL in males, $<$12 ng/mL in females), age $>$ 6 months, and one or more metabolic abnormalities including diabetes mellitus defined per 2007 American Diabetes Association criteria (24), insulin resistance (fasting insulin $\geq$ 30 μU/mL [215 pmol/liter]), or hypertriglyceridemia (fasting triglyceride $>$ 200 mg/dL). Exclusion criteria were pregnancy, infectious liver disease or alcohol abuse, HIV infection, active tuberculosis (TB), hypersensitivity to E. coli derived proteins, use of anorexigenic medications, and psychiatric disorders or other diseases impeding competence or compliance.

Study intervention and follow up

Patients received self-administered subcutaneous meterleptin injections in one to two daily doses ranging from 0.06 to 0.24 mg/kg/d. Doses were adjusted to achieve metabolic control and avoid excessive weight loss. Antihyperglycemic and lipid-lowering regimens were modified if clinically indicated. 103 patients were enrolled. We excluded from analysis four patients with atypical progeroid lipodystrophy, one patient with no baseline data, one who died from pancreatitis and sepsis 3.5 months after the start of meterleptin, one who was taken off meterleptin for a serious adverse event before any follow up was obtained, and 10 who had not yet reached 6 months of meterleptin at the time of the data cut.

Outcome measures

Clinical values were collected at baseline, 6 months (range 4–8 months), and 12 months (range 10–15 months) after meterleptin initiation. Outcomes included serum leptin, anthropometric parameters (body mass index (BMI) [BMI] and body fat percent), glycemic variables (serum glucose, A1c, number of antidiabetic and lipid-lowering medications, insulin use and aver-

age daily insulin dose among insulin users), and lipids. Blood samples were analyzed using the standard techniques of the NIH Clinical Center laboratory. Leptin was measured by radioimmunoassay (RIA) using a commercial kit (Linco Research). Body fat percent was measured using whole body dual energy x-ray absorptiometry (DXA) (Hologic QDR 4500; Hologic, Bedford, MA). BMI was adjusted for sex and age using standard deviation scores (SDS) derived from NHANES population normative data (25). For patients under age 20 years, SDS are Z-scores (compared to age-matched controls). For patients over age 20 years, SDS are T-scores (compared to 20 year-old controls). Compliance was defined as > 70% use of meterleptin injections. The following categories were selected for subgroup analysis in GLD and PLD: baseline triglyceride level ≥ 300 mg/dL, <300, ≥500, and < 500, as well as baseline A1c ≥ 7%, <7, ≥8, and < 8. All GLD patients had leptin levels < 4ng/mL except for one with 5.29ng/mL, therefore subgroup analysis for baseline leptin above or less than 4 ng/mL was performed in PLD only.

Statistical analysis

Statistical analyses were performed using Excel, GraphPad Prism 6.01 (La Jolla, CA) and SAS Enterprise Guide 5.1 (Cary, NC). Baseline characteristics of GLD vs PLD, and change in number of antidiabetic medications and insulin use at 0 months vs 12 months on meterleptin were compared using chi square test for categorical parameters and unpaired or paired Student's *t* tests or age- and sex-adjusted analysis of covariance (ANCOVA) for continuous variables. Triglycerides were log transformed for analyses due to non-normal distribution in lipodystrophic subjects. The relationship between leptin level and body fat, triglycerides and A1c was assessed by linear regression, with adjustment for age as appropriate. Mixed models were used to analyze the change of selected variables over time in response to meterleptin. Univariate and multivariate analyses were used to assess the influence of lipodystrophy type (generalized vs partial) and baseline leptin as potential predictors of meterleptin response. Results are presented as mean ± standard deviation (SD). Triglycerides are presented as geometric means [25th, 75th percentile]. *P*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Patients' baseline characteristics are shown in Table 1 and Figure 1. 55 GLD (39 congenital, 16 acquired) and 31 PLD patients (25 congenital, 6 acquired) were included in the analysis. There were different sex and age distributions

Table 1. Baseline Values in Patients with Generalized *vs.* Partial lipodystrophy

Clinical Values	Generalized Lipodystrophy (*n* = 55)	Partial Lipodystrophy (*n* = 31)	*P* value
Demographic parameters			
Females	42 (76%)	31 (100%)	0.003
Age (years)	18 (12)	35 (14)	<0.001
Pediatric patients (age<20y), %	42 (76%)	7 (23%)	<0.001
Anthropometric parameters			
BMI-Z	0.26 (0.98)	0.66 (0.70)	0.004
Percent body fat	9 (2)	22 (4)	<0.001
Leptin (ng/mL)	1.13 (0.74)	6.23 (3.96)	<0.001
Glycemic parameters			
Glucose (mg/dL)	180 (80)	182 (87)	0.50
A1c (%)	8.4 (2.3)	8.1 (2.2)	0.65
Fasting insulin (mcU/mL)*	122 (318)	82 (157)	0.46
C-peptide (ng/mL)	5.61 (4.03)	3.56 (2.27)	0.21
Anti-diabetic medications per patient	1.13 (0.70)	1.79 (0.68)	<0.001
Insulin users			
Yes	30 (56%)	15 (52%)	0.82
No	24 (44%)	14 (48%)	
Daily total insulin units per patient	625 (1099)	278 (214)	0.12
Lipid parameters			
Lipid lowering medications per patient	0.61 (0.84)	1.07 (1.04)	0.05
Total cholesterol (mg/dL)	214 (110)	235 (147)	0.18
Triglycerides (mg/dL)	467 (200 847)	483 (232, 856)	0.23
HDL-C (mg/dL)	29 (9)	31 (9)	0.33
LDL-C (mg/dL)	104 (50)	101 (36)	0.73
Fat-soluble vitamins			
Vitamin A (mcg/dL)	57 (33) (*n* = 19)	73 (20) (*n* = 13)	0.34
Vitamin E (mg/liter)	26 (32) (*n* = 20)	34 (21) (*n* = 13)	0.25
25-OH vitamin D (ng/mL)	16 (11) (*n* = 46)	23 (13) (*n* = 29)	0.41
PT (seconds)	14.2 (1.2) (*n* = 30)	13.2 (0.6) (*n* = 21)	0.003
INR	1.10 (0.14) (*n* = 22)	0.98 (0.06) (*n* = 16)	0.01

Data are mean (SD), or n (%). Data are geometric mean (25th, 75th percentile) for triglycerides. *Fasting insulin levels in both insulin users and non-users. BMI-Z = body mass index z-score. HDL-C = high density lipoprotein cholesterol. LDL-C = low density lipoprotein cholesterol. PT = prothrombin time. INR = international ratio.

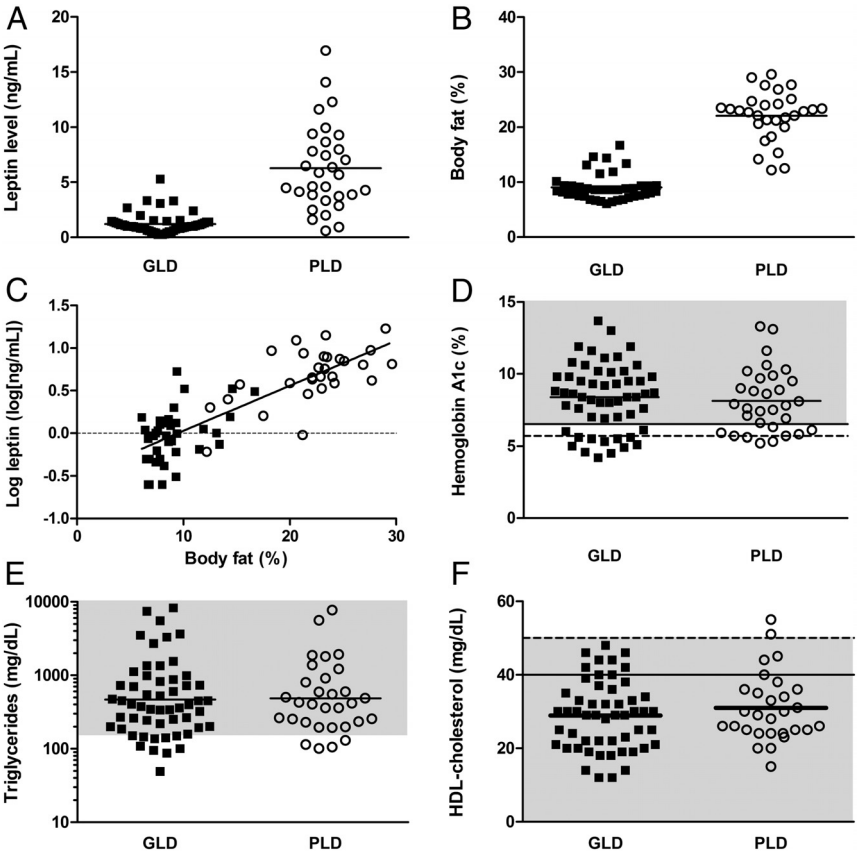

Figure 1. Baseline Values in Patients with Generalized vs Partial lipodystrophy. Baseline subject-level data and means in patients with generalized (GLD, black squares) and partial lipodystrophy (PLD, open circles). Leptin levels (A) and body fat (B) were lower in GLD, and leptin was correlated with body fat (D) in both groups. A1c (D), triglycerides (E, geometric mean), and HDL-C were similar in both groups (high-risk ranges shown in gray shading). Cutoffs for diabetes (solid line), prediabetes (dashed line) (C), and high-risk HDL-C in men (dashed line) and women (solid line) (F) are shown as horizontal lines.

in GLD vs. PLD (76% vs. 100% females, $P = .003$, age 18 ± 12 years [range 1.6–68] in GLD vs. 35 ± 14 [range 11–64] in PLD, $P < .001$). BMI-SDS and percent body fat were significantly lower in GLD. Endogenous leptin was lower in GLD (1.13 ± 0.74 ng/mL, range 0.25–5.29) vs PLD (6.23 ± 3.96 ng/mL, range 0.61–16.93) ($P < .001$), but there was considerable overlap between the two groups. In GLD, leptin levels were similar in males and females (males, 1.08 ± 0.80 ng/mL, N = 13, normal 3.8 ± 1.8 for lean men; females, 1.24 ± 0.93, N = 42, normal 7.4 ± 3.7 for lean women; $P = .55$) (26). In the full cohort (PLD + GLD), leptin correlated with body fat ($r^2 = 0.7$, $P < .001$), similar to the general population (27).

Despite differences in body fat and leptin levels, metabolic parameters including glycemic values and lipids were similar in GLD and PLD. In the full cohort, age-adjusted linear regression showed no correlation between baseline leptin and triglycerides ($P = .96$), or between leptin and A1c ($P = .92$).

Mean levels of the fat-soluble vitamins A, D and E were higher in PLD, consistent with higher fat storage, however these differences were not statistically significant. The prothrombin time and INR, representing vitamin K function, were significantly lower in PLD, also consistent with more adipose storage.

Response to treatment with Meterleptin

Changes in metabolic parameters and use of antidiabetic or lipid lowering medications in response to meterleptin are shown in Table 2, Figure 2 and Supplemental

Table 2. Clinical Values in Generalized and Partial Lipodystrophy Patients Treated with Metreleptin

Clinical Values	Generalized Lipodystrophy				Partial Lipodystrophy			
	0 months (n = 55)	6 months (n = 49)	12 months (n = 52)	P value	0 months (n = 31)	6 months (n = 25)	12 months (n = 28)	P value
Anthropometric parameters								
BMI-Z	0.26 (0.98)	−0.24 (1.35)	−0.33 (1.20)	<0.001	0.66 (0.70)	0.49 (0.76)	0.50 (0.76)	0.01
Percent body fat	9 (2)	8 (2)	8 (2)	0.09	22 (4)	20 (4)	18 (3)	0.07
Glycemic parameters								
Glucose (mg/dL)	180 (80)	124 (50)	121 (60)	<0.001	182 (87)	137 (43)	132 (54)	<0.001
A1c (%)	8.4 (2.3)	6.6 (1.7)	6.4 (1.5)	<0.001	8.1 (2.2)	7.2 (1.2)	7.3 (1.6)	0.004
C-peptide (ng/mL)	5.61 (4.03)	4.23 (2.77)	4.48 (3.09)	0.01	3.56 (2.27)	3.76 (1.96)	3.41 (1.94)	0.26
Anti-diabetic medications per patient	1.13 (0.70)		0.65 (0.62)	<0.001	1.79 (0.68)		1.74 (0.81)	0.42
Insulin use	28 (55%)		11 (21%)	<0.001	14 (52%)		14 (52%)	1.00
Yes	23 (45%)		41 (79%)		13 (48%)		13 (48%)	
No								
Daily total insulin units per patient	625 (1099)		103 (398)	0.009	278 (214)		175 (131)	0.07
Lipid parameters								
Lipid lowering medications per patient	0.61 (0.84)		0.27 (0.53)	<0.001	1.07 (1.04)		1.08 (1.09)	1.0
Total cholesterol (mg/dL)	214 (110)	146 (58)	146 (38)	<0.001	235 (147)	188 (45)	196 (73)	0.06
Triglycerides (mg/dL)	467 (200 847)	198 (122, 283)	180 (106, 312)	<0.001	483 (232, 856)	339 (211, 530)	326 (175, 478)	0.02
HDL-C (mg/dL)	29 (9)	30 (8)	30 (7)	0.78	31 (9)	33 (7)	32 (9)	0.32

Data are mean (SD), or n (%). Data are geometric mean (25th, 75th percentile) for triglycerides. P value is for the effect of metreleptin over time. BMI-Z = body mass index z-score. HDL-C = high density lipoprotein cholesterol.

Table 1. Over 12 months of meterleptin treatment, BMI-SDS significantly decreased in both GLD and PLD, but remained within the normal range. Body fat was similar at baseline and 12 months in GLD, but showed a nonsignificant downward trend in PLD. 88% and 82% of GLD patients were compliant to treatment at 6 and 12 months, respectively. 80% and 75% of PLD patients were compliant to treatment at 6 and 12 months, respectively. A1c fell from 8.4 ± 2.3% at baseline to 6.4 ± 1.5% at 12 months in GLD ($P < .001$ for change in A1c over time), and from 8.1 ± 2.2% to 7.3 ± 1.6% in PLD ($P = .004$). Improvements in A1c with meterleptin were significantly greater in GLD compared to PLD. Similarly, fasting glucose decreased in both GLD and PLD (180 ± 80 mg/dL to 121 ± 60 in GLD, 182 ± 87 to 132 ± 54 in PLD, $P < .001$). The number of antidiabetic and lipid-lowering medications per patient, rate of insulin users and total daily insulin dose were significantly lower in GLD after 12 months on meterleptin. These measures did not change in PLD, though there was a trend for lower daily insulin dosing (278 ± 214 U at 0 months to 175 ± 131 at 12 months, $P = .07$). In GLD, 14 patients stopped or reduced the dose of lipid lowering medications, 6 had no change, and none increased the dose or number of medications. In PLD, 2 patients stopped or reduced the dose of lipid lowering medications, 12 had no change, and 2 added a lipid lowering medication to their baseline regimen. Meterleptin resulted in significant reductions in triglycerides in GLD (geometric mean [25th, 75th percentile], 467 mg/dL (200, 847) at baseline to 180 mg/dL (106, 312) at 12 months, $P < .001$) and PLD (483 mg/dL (232, 856) at baseline to 326 mg/dL (175, 478) at 12 months, $P = .02$). There was a decrease in total cholesterol in GLD ($P < .001$) and PLD ($P = .06$), whereas HDL-C did not change. Most the change in A1c and triglycerides was already noted after 6 months of treatment. Neither of these outcomes was different at 6 vs 12 months on post hoc testing in both GLD and PLD. Both A1c change and triglyceride change over time were significantly different in PLD vs

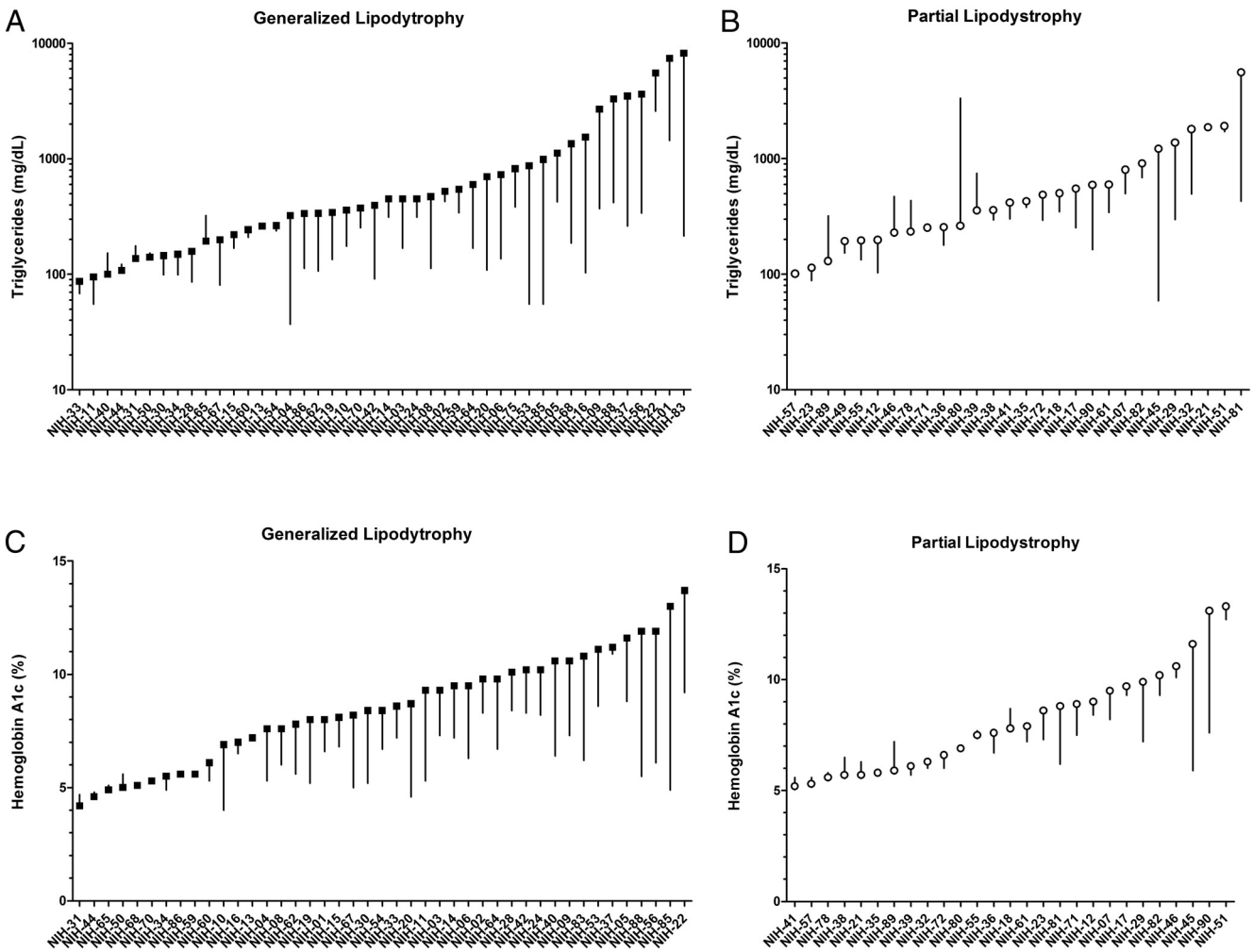

Figure 2. Clinical Values in Generalized and Partial Lipodystrophy Patients Treated with Meterleptin. Waterfall plots showing change in triglycerides and hemoglobin A1c in individual subjects (subject identifier on X-axis) after one year of meterleptin in generalized (A and C, black squares) and partial (B and D, open circles) lipodystrophy patients.

GLD patients treated with meterleptin ($P = .0004$ and $P = .0272$, respectively).

Subgroup analyses

Subgroup analyses are shown in Tables 3 and 4. The decrease in A1c and in triglycerides in response to meterleptin was statistically significant in PLD patients with the following characteristics: baseline triglycerides ≥ 300 mg/dL or ≥ 500 mg/dL, baseline A1c ≥ 7% or ≥ 8%, and baseline leptin < 4 ng/mL. In contrast, meterleptin did not lower A1c or triglycerides in PLD patients with baseline triglycerides < 300 mg/dL or < 500 mg/dL, baseline A1c < 8% or baseline leptin ≥ 4ng/mL.

In GLD, the decrease in A1c with meterleptin was statistically significant in all subgroups. The meterleptin-induced decrease in triglycerides was statistically significant in all subgroups except in patients with baseline triglycerides < 300 mg/dL.

Predictors of response to meterleptin

Univariate analysis in the full cohort showed that both lipodystrophy type (generalized vs. partial) and the baseline endogenous leptin level predicted the triglyceride response to meterleptin ($P = .006$ for lipodystrophy type, $P < .001$ for baseline leptin). Lipodystrophy type was significant ($P = .001$) and baseline leptin was borderline significant ($P = .05$) in predicting the A1c response to meterleptin. Sex, age, race, compliance to meterleptin, baseline BMI-Z or BMI-Z change on treatment were not significant predictors of either triglyceride or A1c response to meterleptin. Multivariate analyses including both lipodystrophy type and baseline leptin as predictors showed that lipodystrophy type was significant in predicting A1c response ($P = .02$ for lipodystrophy type, $P = .57$ for baseline leptin) whereas baseline leptin predicted triglyceride response to meterleptin ($P = .20$ for lipodystrophy type, $P = .03$ for baseline leptin).

Adverse events

During 12 months of treatment with meterleptin 275 adverse events (AEs) occurred, including 21 serious AEs (SAEs) in 10 patients. All SAEs were judged to be unrelated to meterleptin treatment. AEs occurring in at least 5% of patients, and all SAEs, are summarized in Supplemental Table 2. The most common AEs were gastrointestinal (GI) (38% of patients), musculoskeletal (22%) and infections (15%).

Discussion

This work shows that meterleptin is an effective treatment in PLD patients with severe metabolic abnormalities or low endogenous leptin in addition to its proven efficacy in GLD. We have demonstrated this effect in the largest cohort of lipodystrophy patients (both PLD and GLD) studied to date. Specifically, the PLD patients most likely to respond are those with triglycerides over 500 mg/dL or A1c over 8%. There were also significant improvements in A1c and triglycerides in PLD patients with endogenous leptin less than 4 ng/mL (comparable to leptin levels seen in GLD), regardless of the severity of their lipid or glucose abnormalities. In addition, there were individual patients who did not meet these criteria who nonetheless showed metabolic improvement with meterleptin.

Patients with lipodystrophy have extreme manifestations of the common, obesity-associated metabolic syndrome. Studies of insulin resistance in patients with obesity-associated metabolic syndrome are hampered by the heterogeneous nature of this condition, which is contributed to by hundreds of genes as well as environmental factors. Lipodystrophy patients, by virtue of their more extreme phenotype, as well as a defined target for intervention (leptin deficiency), serve as models to understand the role of leptin in human energy metabolism. By advancing our understanding of pathways regulating energy metabolism in rare diseases, we can not only develop therapeutics for these rare conditions, but also elucidate pathways that may serve as drug targets for more common disorders of insulin resistance. Meterleptin has not been effective in reducing insulin resistance in obese subjects with type 2 diabetes (28), likely due to insensitivity to added, recombinant leptin in patients with already high endogenous leptin produced by large adipose tissue depots. However, meterleptin may have clinical utility in

Table 3. Subgroup analysis of the change in hemoglobin A1c in response to metreleptin treatment in GLD and PLD patients

Subgroup	Generalized Lipodystrophy				Partial Lipodystrophy			
	0 month A1c (%)	6 months A1c (%)	12 months A1c (%)	P value	0 months A1c (%)	6 months A1c (%)	12 months A1c (%)	P value
Baseline A1c>8% (GLD *n* = 34; PLD *n* = 14)	9.8 (1.4)	7.1 (1.8)	6.9 (1.5)	<0.001	10.1 (1.6)	7.9 (1.2)	8.3 (1.9)	<0.001
Baseline A1c>7% (GLD *n* = 40; PLD *n* = 20)	9.4 (1.6)	7.0 (1.7)	6.8 (1.5)	<0.001	9.3 (1.8)	7.8 (1.1)	8.1 (1.7)	0.002
Baseline A1c<8% (GLD *n* = 22; PLD *n* = 17)	6.1 (1.2)	5.6 (1.1)	5.5 (0.8)	0.002	6.5 (0.9)	6.8 (1.2)	6.5 (0.9)	0.81
Baseline leptin <4 ng/mL (PLD *n* = 10)					8.8 (2.6)	7.1 (1.7)	7.3 (2.2)	0.04
Baseline leptin >4 ng/mL (PLD *n* = 21)					7.8 (2.0)	7.3 (1.1)	7.3 (1.4)	0.15

Data are mean (SD), or n (%). P value is for the effect of metreleptin over time.

Table 4. Subgroup analysis of the change in triglycerides in response to metreleptin treatment in GLD and PLD patients

Subgroup	Generalized Lipodystrophy				Partial Lipodystrophy			
	0 month triglycerides (mg/dL)	6 months triglycerides (mg/dL)	12 months triglycerides (mg/dL)	P value	0 months triglycerides (mg/dL)	6 months triglycerides (mg/dL)	12 months triglycerides (mg/dL)	P value
Baseline triglycerides >300 mg/dL (GLD *n* = 34; PLD *n* = 19)	912 (449, 1347)	257 (148, 334)	208 (113, 341)	<0.001	926 (457, 1590)	410 (238, 596)	396 (295, 498)	0.002
Baseline triglycerides >500 mg/dL (GLD *n* = 22; PLD *n* = 13)	1455 (728, 3153)	308 (150, 597)	264 (144, 410)	<0.001	1309 (598, 1863)	429 (223, 623)	405 (285, 545)	0.001
Baseline triglycerides <300 mg/dL (GLD *n* = 21; PLD *n* = 12)	158 (137, 220)	131 (97, 205)	135 (93, 193)	0.28	179 (126, 239)	254 (173, 287)	241 (118, 377)	0.51
Baseline triglycerides <500 mg/dL (GLD *n* = 33; PLD *n* = 18)	219 (149, 343)	150 (123, 230)	138 (99, 201)	<0.001	235 (194, 359)	290 (206, 409)	277 (148, 392)	0.71
Baseline leptin <4 ng/mL (PLD *n* = 10)					978 (513, 1848)	429 (215, 629)	342 (179, 498)	0.04
Baseline leptin >4 ng/mL (PLD *n* = 21)					345 (198, 503)	297 (209, 380)	318 (200, 432)	0.42

Data are geometric mean (25th, 75th percentile). P value is for the effect of metreleptin over time.

other common disorders, such as patients with nonalcoholic steatohepatitis and relatively low leptin levels (29).

At baseline, PLD patients were older than GLD patients, presumably because metabolic complications of lipodystrophy present at a younger age in GLD. By the time of study enrollment, both groups had comparable metabolic disease severity, showing that, over time, PLD manifestations may be as severe as those seen in GLD. The similarity in baseline metabolic disease is particularly notable given that, as expected, PLD patients had higher BMI, body fat, and leptin levels than GLD patients. Moreover, there was no correlation between the severity of metabolic disease at baseline and endogenous leptin levels. Of note, our cohort is biased toward more severe metabolic disease in both GLD and PLD due to study inclusion criteria; however, the PLD cohort is likely to be more biased, as it is not uncommon for PLD patients to present with the characteristic physical phenotype but only minimal metabolic derangements.

Given the inherent differences in body fat in GLD and PLD, we hypothesized that fat-soluble vitamins would be lower in GLD. Consistent with this, all vitamin levels were higher in PLD patients, although only PT and INR (markers of vitamin K) achieved statistical significance. The failure to detect significant differences in vitamins A, D, and E may be attributable to small sample size; however, none of the differences in fat-soluble vitamins appeared to be clinically significant. In fact, prior studies have shown elevated bone mineral content despite low vitamin D stores in congenital generalized lipodystrophy (30).

In studying predictors of response to meterleptin, we focused on hypertriglyceridemia and diabetes, which are a major source of morbidity and mortality in this population, and are difficult to control with conventional treatments. Our findings indicate significant improvements in these values in response to meterleptin in both GLD and PLD, with much of the effect seen after 6 months of treatment. With meterleptin, GLD patients required significantly less pharmacological intervention to achieve better control of diabetes, whereas PLD patients achieved better control on the same antidiabetic regimen. The dramatic 73% reduction in triglycerides and 2% point reduction in A1c in GLD are consistent with prior reports (14–19, 21–23). In PLD, meterleptin decreased triglycerides by 54% and A1c by 0.8%. Two prior small studies of PLD (N = 6 from NIH, a subgroup of the current analyses (22) and N = 24 from University of Texas Southwestern (23)) showed improvements in hypertriglyceridemia but no change in A1c with meterleptin. The Texas cohort had much milder metabolic abnormalities at baseline compared to NIH subjects (mean A1c 6.5 ± 1.7%, median TG 287 mg/dL), likely explaining the lack of significant meterleptin response. Moreover, a post hoc analysis of the Texas cohort revealed significant A1c lowering in patients with A1c above 6.5%, supporting the idea that patients with more severe baseline disease are more likely to improve with meterleptin. Overall, our findings indicate significant improvements in hypertriglyceridemia and diabetes in response to meterleptin in both GLD and PLD, with much of the effect seen after 6 months of treatment. The meterleptin-induced 0.8%–2% reduction in A1c is comparable to the extent of A1c improvement by conventional antidiabetic medications.

In our analysis, meterleptin was not effective in PLD patients with mild disease, namely triglycerides less than 500 mg/dL or A1c less than 8%. In contrast, in GLD, meterleptin was effective across a wider range of severity of baseline metabolic derangements. It reduced A1c in all analyzed subgroups, and ameliorated hypertriglyceridemia in all cases except patients with baseline triglycerides less 300 mg/dL. These findings attest to the need for proper selection of patient populations in whom meterleptin would be effective. In other words, meterleptin is effective not only in GLD, but also may be of benefit for PLD patients with severe metabolic abnormalities.

Another predictor for A1c and triglyceride response to meterleptin in PLD was the endogenous leptin level at baseline, as meterleptin was effective only in patients with very low leptin (<4ng/mL), comparable to that found in GLD. This brought about a question of the significance of the lipodystrophy type (generalized vs. partial) vs the endogenous leptin level in predicting effects of meterleptin on metabolic disease. Univariate and multivariate analyses suggested that lipodystrophy type is significant in predicting A1c, but not triglyceride response, whereas baseline leptin predicts triglyceride, but not A1c response to

meterleptin. These results should be interpreted cautiously, as lipodystrophy type and leptin levels partially cosegregate (GLD overlapping with low leptin and PLD with higher leptin).

Despite the difference in compliance rates between GLD and PLD patients, it was not found to predict the response to treatment. The categorical measurement of compliance (>70% of doses taken) may not have been sensitive enough to detect effects of compliance on metabolic response.

An analysis of risks and benefits must be considered prior to any medication's approval by the FDA. No serious adverse events that were judged to be related to treatment occurred in this cohort. During long term uncontrolled studies of meterleptin in lipodystrophy, the occurrence of three cases of T-cell lymphoma and four cases of neutralizing antibodies to leptin (unpublished data) resulted in black box warnings on the meterleptin package insert.

To conclude, we clearly show a beneficial effect of meterleptin on glycemic and lipid measures in both GLD and PLD, especially in a selected cohort of PLD patients with significant metabolic abnormalities. The absolute improvement in metabolic abnormalities in PLD patients should be regarded independently, without a comparison to the somewhat higher efficacy of meterleptin in GLD. Due to the rarity of lipodystrophy, long-term studies powered to detect changes in mortality, cardiovascular, and microvascular disease endpoints are unlikely to be performed. The clinically and statistically significant effects of meterleptin in PLD shown here will likely affect patient outcomes in long term surveillance.

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